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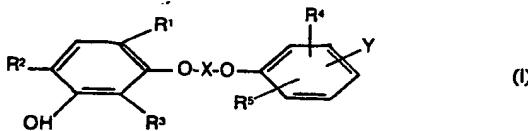
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(54) Phenol derivatives, processes for their preparation and pharmaceutical compositions containing them.

(57) Compounds are disclosed which are phenoxyalkoxyphenyl derivatives of general formula (I)



hydrogen atom, an aryl group or a C₁₋₆ alkyl group which may be substituted by an aryl group;

R³ represents a C₁₋₆ alkyl group or a C₃₋₆ alkenyl group; and

R⁴ and R⁵ which may be the same or different, each represents a hydrogen atom, a halogen atom or a hydroxy, C₁₋₃ alkoxy, C₁₋₆ alkyl, C₃₋₆ alkenyl, C₁₋₃ alkanoyl, nitro or carboxylic acid group with the proviso that R⁴ and R⁵ cannot both be nitro, alkanoyl or carboxylic acid groups, and physiologically acceptable salts thereof.

The compounds are potent antagonists of the action of slow reacting substance of anaphylaxis and are thus indicated for use in the treatment of obstructive airways diseases such as asthma and hay fever and in skin afflictions.

A1

wherein

Y represents the group -A, -ZA or OZ'A where A represents a carboxylic acid group, a 5-1H-tetrazolyl ring or a N-5-1H-tetrazolylcarboxamide group;

Z represents a C₁₋₄ alkylenes, C₂₋₄ alkenylene or C₂₋₄ alkylenylene chain optionally substituted by one or more C₁₋₃ alkyl groups and Z' represents a C₁₋₄ alkylenes chain optionally substituted by one or more C₁₋₃ alkyl groups;

X represents a C₁₋₁₀ carbon chain which may be saturated or unsaturated in the case of chains containing at least 4 carbon atoms, and may be substituted by a hydroxy group or by one or more C₁₋₃ alkyl groups, which chain may be interrupted by a benzene ring which may be linked through its 1- and 2-, 1- and 3-, or 1- and 4-positions;

R¹ represents a hydrogen atom or a C₁₋₆ alkyl group;

R² represents the group -COR⁶ where R⁶ represents a

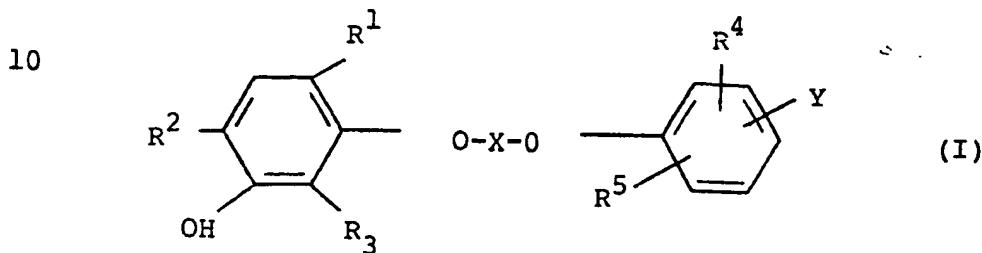
EP 0028063

Phenol derivatives, processes for their preparation and pharmaceutical compositions containing them

This invention relates to phenol derivatives, to processes for their preparation and to pharmaceutical compositions containing them.

More particularly, this invention relates to
5 phenoxyalkoxyphenyl derivatives and processes for their preparation.

The invention provides a compound of the general formula (I)



15 and physiologically acceptable salts thereof.

In the general formula (I),

Y represents the group $-A$, $-ZA$ or OZ^1A where

A represents a carboxylic acid group, a 5-1H-tetrazolyl ring, or N-5-1H-tetrazolylcarboxamide group;

20 Z represents a C_{1-4} alkylene, C_{2-4} alkenylene or C_{2-4} alkynylene chain optionally substituted by one or more C_{1-3} alkyl groups and Z^1 represents a C_{1-4} alkylene chain optionally substituted by one or more C_{1-3} alkyl groups;

25 X represents a C_{1-10} carbon chain which may be saturated or unsaturated in the case of chains containing at least 4 carbon atoms, and may be substituted by a hydroxy group or by one or more C_{1-3} alkyl groups, which chain may be interrupted by a benzene ring which may be

30 linked through its 1- and 2-, 1- and 3-, or 1- and 4-positions;

R^1 represents a hydrogen atom or a C_{1-6} alkyl group;

R^2 represents the group $-COR^6$ where R^6 represents a hydrogen atom, an aryl group or a C_{1-6} alkyl group which

may be substituted by an aryl group;

R³ represents a C₁₋₈ alkyl group or a C₃₋₆ alkenyl group;

and

5 R⁴ and R⁵, which may be the same or different, each represents a hydrogen atom, a halogen atom or a hydroxy, C₁₋₃ alkoxy, C₁₋₆ alkyl, C₃₋₆ alkenyl, C₁₋₃ alkanoyl, nitro or carboxylic acid group, with the proviso that R⁴ and R⁵ cannot both be nitro, alkanoyl
10 or carboxylic acid groups.

Referring to the general formula (I), the alkyl group represented by R¹, R², R³, R⁴ and R⁵ and the alkenyl groups represented by R³, R⁴ and R⁵ may be a straight chain or branched chain group.

15 When Y is the group A, A preferably represents a carboxylic acid group or a 5-1H-tetrazolyl ring.

When Y is the group ZA or OZ¹A, A preferably represents a carboxylic acid group, Z preferably represents a C₁₋₄ alkylene chain, particularly

20 methylene or ethylene, or a C₂₋₄ alkenylene chain, particularly ethenylene, or a C₂₋₄ alkynylene chain, particularly ethynylene, and Z¹ preferably represents methylene.

Examples of the group X are a straight carbon chain of formula (CH₂)_n where n is a number from 1 to 25 10, or a group of formula -CH₂X¹CH₂- where X¹ is a benzene ring linked through its 1- and 2-, 1- and 3-, or 1- and 4-positions. X preferably represents a group of formula (CH₂)_n where n is 1, 3 or 5.

30 R¹ preferably represents a hydrogen atom or a C₃₋₆ alkyl group, particularly propyl.

R² is preferably the group COR⁶ where R⁶ represents a C₁₋₆ alkyl group, particularly a methyl group. When R⁶ is an aryl group it is, for example, 35 a phenyl group.

R³ preferably represents a C₃₋₆ alkyl group,

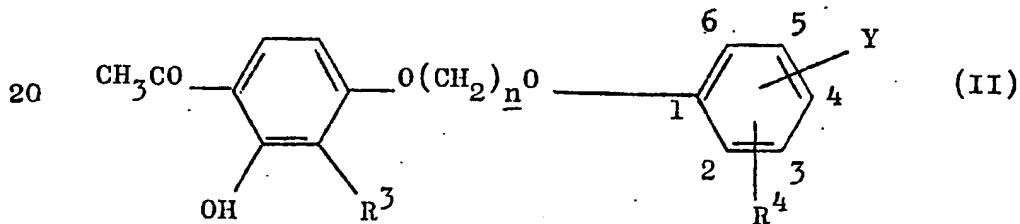
particularly propyl, or C₃₋₆ alkenyl group, particularly propenyl.

5 R⁴ preferably represents a hydrogen or halogen atom, or a hydroxy, nitro or C₁₋₃ alkanoyl group. When R⁴ is a halogen atom it is preferably bromine. The C₁₋₃ alkanoyl group represented by R⁴ is preferably acetyl.

10 R⁵ is preferably a hydrogen atom or a C₁₋₆ alkyl group, particularly propyl, or a C₂₋₄ alkenyl group, particularly propenyl.

Particularly preferred compounds are those in which R⁴ is a hydrogen atom or a hydroxyl group and R⁵ is a hydrogen atom.

15 A preferred group of compounds are those of formula (II):-



25 where Y is a carboxylic acid group or a 5-1H-tetrazolyl ring or a N-5-1H-tetrazolylcarboxamide group, or a C₁₋₂ alkyl, C₁₋₂ alkoxy or C₂-alkenyl chain terminally substituted by a carboxylic acid group, and is preferably situated at the 3- or 4-position in the benzene ring;

30 n is 1, 3 or 5, preferably 3,

R³ is a C₃₋₆ alkyl or C₃₋₆ alkenyl group,

R⁴ is a hydrogen or bromine atom, or a hydroxy, nitro or acetyl group,

and physiologically acceptable salts thereof.

35 In formula (II), when R⁴ is a hydroxy group it is preferably situated adjacent to the group Y.

Preferred salts of the above acids include salts obtained by reaction with an inorganic or organic base, for example sodium salts or salts with ethylenediamine.

5 Particularly preferred compounds according to the invention include:

- 4-[3-(4-Acetyl-3-hydroxy-2-propylphenoxy)propoxy]-2-hydroxybenzoic acid;
- 10 3-[3-(4-Acetyl-3-hydroxy-2-propylphenoxy)propoxy]benzoic acid;
- 3-[4-[3-(4-Acetyl-3-hydroxy-2-propylphenoxy)-propoxy]phenyl]-2-propenoic acid;
- 4-[3-(4-Acetyl-3-hydroxy-2-propylphenoxy)propoxy]benzoic acid;
- 15 3-[3-(4-Acetyl-3-hydroxy-2-propylphenoxy)propoxy]benzenepropanoic acid;
- 2-[4-[3-(4-Acetyl-3-hydroxy-2-propylphenoxy)propoxy]phenoxy]acetic acid;
- 3-[3-[3-(4-Acetyl-3-hydroxy-2-propylphenoxy)propoxy]-phenyl]-2-propenoic acid;
- 20 4-[3-(4-Acetyl-3-hydroxy-2-propylphenoxy)propoxy]-2-hydroxy-3-propylbenzoic acid;
- 3-[5-[3-(4-Acetyl-3-hydroxy-2-propylphenoxy)propoxy]-2-bromophenyl]-2-propenoic acid;
- 25 3-[3-[5-(4-Acetyl-3-hydroxy-2-propylphenoxy)pentyloxy]phenyl]-2-propenoic acid;
- 3-[3-[3-[4-Acetyl-3-hydroxy-2-propylphenoxy]propoxy]-4-nitrophenyl]-2-propenoic acid;
- 3-[3-[3-[4-Acetyl-3-hydroxy-2-propylphenoxy]propoxy]-4-acetylphenyl]-2-propenoic acid;
- 30 5-[3-[3-[4-Acetyl-3-hydroxy-2-propylphenoxy]propoxy]phenyl]-1H-tetrazole;
- 3-[3-[3-[4-Acetyl-3-hydroxy-2-[2-propenyl]phenoxy]propoxy]phenyl]-2-propenoic acid;
- 35 3-[3-[3-[4-Acetyl-3-hydroxy-2-(1-methylpropyl)phenoxy]propoxy]phenyl]-2-propenoic acid;

and the physiologically acceptable salts of these compounds.

The invention also extends to all possible enantiomers and diasteriomers of the compounds

5 according to the formula (I).

The compounds according to the invention are potent antagonists of the action of slow reacting substance of anaphylaxis (SRS-A) as shown by their ability to inhibit the SRS-A induced contraction of
10 guinea pig ileum (Coleman *et al*, Br. J. Pharmacol., 1979, 66, 83P). SRS-A is a naturally occurring substance which causes contraction of smooth muscle, especially bronchial muscle, and increases vascular permeability. The substance is not normally present
15 in human tissue but is synthesised and released from certain cells during an allergic reaction. The compounds according to the invention are thus indicated for use in the treatment of disorders in which SRS-A may be a factor, for example, in obstructive airways
20 diseases such as asthma, in hay fever and in skin afflictions.

The compounds according to the invention may be formulated for use in human or veterinary medicine for therapeutic or prophylactic purposes. The invention
25 therefore includes within its scope pharmaceutical compositions comprising as active ingredients one or more compounds selected from compounds of general formula (I) and physiologically acceptable addition salts thereof. Such compositions may be presented for
30 use in a conventional manner with the aid of physiologically acceptable carriers or excipients and formulatory agents as required, and with or without supplementary medicinal agents. These compositions include, for instance, tablets, suppositories,
35 injections and forms suitable for administration by inhalation. Injections may be formulated with the aid

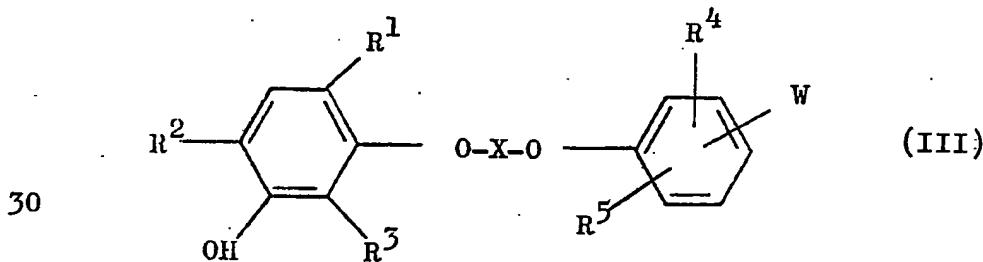
of physiologically acceptable carriers and agents as solutions, suspensions, or as dry products for reconstitution before use.

For administration by inhalation the compounds
5 are conveniently delivered in the form of an aerosol spray presentation from pressurised packs or a nebuliser. The preferred composition for inhalation is a powder which may be formulated as a cartridge from which the powdered composition may be inhaled
10 with the aid of a suitable device. In the case of a pressurised aerosol the dosage unit may be determined by providing a valve to deliver a metered amount.

The doses of the active ingredient which may be used vary within a wide range. Suitable dosage
15 units are generally within the range of 50 mg to 1000 mg/day which may be conveniently administered in two or three daily doses. The precise dose administered will always depend on the age and condition of the patient.

20 The compounds according to the invention may be prepared by a number of processes. According to one embodiment of the invention compounds of formula (I) may be prepared from the corresponding compounds of general formula (III):

25



in which

35 R¹ to R⁵ and X are as previously defined and
W represents -CHO, -E,
-ZE or OZ¹E in which Z and Z¹ are as previously defined and E represents a group which is

convertible to the group A previously defined, such as a carboxylic ester, carboxamide or nitrile group.

Thus, for example, a compound of the general formula (I) in which -Y represents the group $-\text{CH}=\text{CHCO}_2\text{H}$ may be prepared from the corresponding compound of general formula (III) in which W represents $-\text{CHO}$, by the Perkin synthesis of cinnamic acids, as described in Organic Reactions, John Wiley & Sons, New York, Vol I, pp 210-10 265.

A compound of general formula (I), in which Y represents the group $-\text{A}$, $-\text{ZA}$ or $-\text{OZ}^1\text{A}$ where Z and Z^1 are as previously defined and A is a carboxylic acid group, may be prepared by acid or basic hydrolysis of the corresponding compound of general formula (III) in which W represents the group $-\text{E}$, $-\text{ZE}$ or $-\text{OZ}^1\text{E}$ where E is a carboxylic ester, amide or nitrile group using standard conditions for example by hydrolysis with an acid such as aqueous sulphuric acid at an elevated temperature, or by hydrolysis with a base such as sodium hydroxide, potassium hydroxide or lithium hydroxide in a solvent such as ethanol, aqueous tetrahydrofuran or water at a temperature of 20 - 100°C.

A compound of general formula (I), in which Y represents the group $-\text{A}$, $-\text{ZA}$ or $-\text{OZ}^1\text{A}$ where Z and Z^1 are as previously defined and A is a 5-1H-tetrazolyl ring, may be prepared from the corresponding compound of general formula (III) in which W represents $-\text{E}$, $-\text{ZE}$ or $-\text{OZ}^1\text{E}$ and E represents a nitrile, using standard conditions, for example using a salt of hydrazoic acid in a solvent such as dimethylformamide or dioxan at an elevated temperature. Suitable salts include sodium or ammonium azide. The reaction may be performed, for example, using sodium azide and ammonium chloride in dimethylformamide at a temperature of 50 to 100°C.

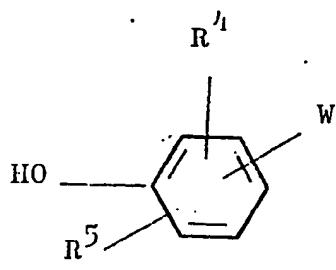
A compound of general formula (I) in which Y

represents the group -A, -ZA or -OZ¹A where Z and Z¹ are as previously defined and A is a carboxylic acid group, may be prepared by hydrogenolysis of the corresponding compound of general formula (III) where W represents the group -E, -ZE, 5 or -OZ¹E where E is a carboxylic ester group of formula COOR⁷ and R⁷ is a group which may be removed by hydrogenolysis, for example an arylmethyl group such as a benzyl or benzhydryl group, using standard conditions, for example in the presence of a catalyst, such as platinum or palladium 10 in a suitable solvent such as an alcohol e.g. ethanol.

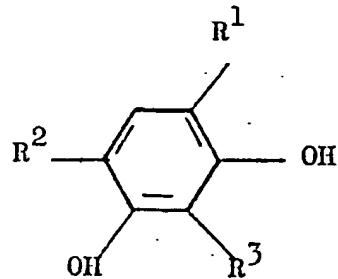
This reaction may be conveniently employed concurrently to reduce other groups in a compound of general formula (III). For example, a compound of general formula (I) in which A is a carboxylic acid group and R³ is a C₂₋₆ 15 alkyl group, such as propyl, may be prepared by catalytic hydrogenation of the corresponding compound of general formula (III) where W represents the group E, ZE or OZ¹E where Z and Z¹ are as previously defined and E is a carboxylic ester group, such as a benzyl ester 20 group, and R³ is a C₂₋₆ alkenyl group, such as propenyl.

The intermediate compounds of formula (III) may be prepared by a number of processes. For example, the compounds of formula (III) may be obtained by 25 alkylation of the corresponding phenols of general formula (IV) or (V):

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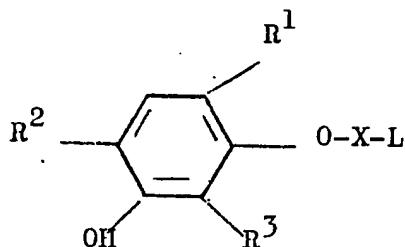


(IV)

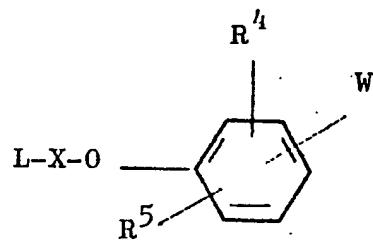


(V)

with an appropriate alkylating agent of formula (VI)
or (VII) respectively,



(VI)



(VII)

in which

L is a leaving group for example a halogen atom
or a paratoluenesulphonate or a methylsulphonate
ester,

in the presence of a base in a suitable solvent, for example sodium hydride in dimethylformamide or potassium carbonate in butanone.

5 The alkylating agents of formula (VI) or (VII) may be prepared from the corresponding phenols of formula (V) or (IV) respectively by treatment with a compound $L - X - L^1$ (where L is a leaving group as previously described and L^1 is the same or different
10 leaving group, or is a group such as hydroxy group which may be converted into a leaving group by conventional methods) in the presence of a base in a suitable solvent as described above for the preparation of compounds of formula (III).

15 The phenols of formulae (IV) and (V) are either known compounds or may be prepared from known starting materials by methods analogous to those used for the preparation of the similar known phenols.

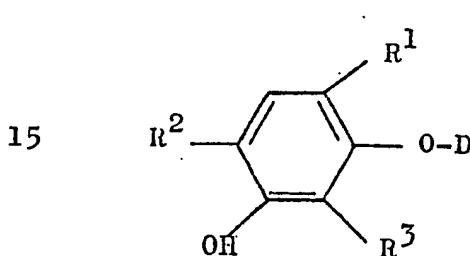
20 For example, phenols of formula (IV) in which W represents the group $-E$, ZE or OZ^1E where Z and Z^1 are as previously described and E is a carboxylic ester group may be prepared using methods similar to that described by Carter and Lawrence, J. Chem. Soc. 77, 1226 (1900), or by esterification of the
25 corresponding acids using standard conditions. The acids are either known or may be prepared from known starting materials by conventional methods for example by the Perkin synthesis as previously described for the preparation of compounds of formula (I).

30 Phenols of formula (V) in which R^1 is a hydrogen atom may, for example, be prepared according to the methods of R.A. Appleton et al J. Med. Chem., 20 371 (1977) or W. Baker and O.M. Lothian in J. Chem. Soc., 628 (1935).

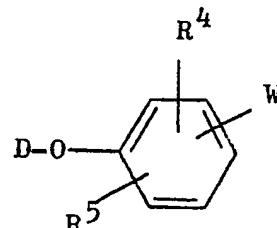
35 It will be appreciated that some of the intermediates of general formula (IV) and (VII) may, if

desired, be modified by electrophilic substitution using standard conditions, for example by nitration with a nitrating agent, such as concentrated nitric acid at low temperatures, or by bromination with a 5 brominating agent, such as N-bromoacetamide in a solvent such as dioxan at an elevated temperature.

A compound of general formula (III) in which the chain -X- is substituted by a hydroxy group may 10 be obtained by reaction of a compound of general formula (VIII) or (IX),



(VIII)



(IX)

20 wherein D represents a hydrocarbon chain carrying an epoxide group, with a phenol of general formula (IV) or (V) respectively in a suitable solvent, for example dimethylformamide, in the presence of a catalyst such as 25 trimethylbenzylammonium hydroxide at an elevated temperature.

An epoxide of formula (VIII) or (IX) may be 30 obtained from a phenol of formula (V) or (IV) respectively by treatment with an alkyl halide carrying an epoxide group, for example epichlorohydrin, in the presence of a base such as potassium carbonate and in a solvent such as butanone.

Certain of the compounds of general formula (I) 35 may be prepared from other compounds of general formula (I). Thus for example compounds of formula (I) in which Y represents the group -ZA where Z is a C₂₋₄ alkylene

or C_{2-4} alkenylene chain may be prepared by catalytic hydrogenation of a corresponding compound of formula (I) where Z is a C_{2-4} alkenylene or C_{2-4} alkynylene chain. Conventional catalysts may be used, preferably 5 palladium in a suitable solvent, for example an alcohol such as methanol.

A compound of general formula (I) in which Y represents the group $-A$, $-ZA$ or OZ^1A where A is a N-5-1H-tetrazolyl-carboxamide may be prepared from the 10 corresponding compounds of formula (I) in which A represents a carboxylic acid group using standard conditions, for example using 5-aminotetrazole and a coupling agent such as N,N'-carbonyldiimidazole in a solvent such as dimethylformamide or tetrahydrofuran.

15 It will be appreciated that certain of the reactions described above are capable of affecting other groups in the starting material which are desired in the end products; care must therefore be taken, in accordance with conventional practice either to perform reactions in 20 a sequence which does not modify groups which are to be retained in the end products, or to ensure that such groups are in protected forms before the start of the reaction.

This applies in particular to the preparation of 25 the intermediates of formula (III) where it may be necessary to protect hydroxyl groups in starting materials (IV) and (VII) which are not involved in the alkylation reaction.

The hydroxy groups may be protected as, for 30 example, a benzyl ether or an acetate during the synthesis. The protecting group is removed when required either by catalytic hydrogenolysis or by hydrolysis as appropriate.

A physiologically acceptable salt of a compound 35 of general formula (I) may be prepared by standard techniques for example by treatment of the free acid of

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formula (I) with a base such as sodium hydroxide.

The following Examples illustrate the invention.
All temperatures are in °C and "petroleum ether" refers
to petroleum ether (b.p. 60-80°).

Preparation 12-Hydroxy-4-(2-propenyl)benzoic acid, methyl ester

Methyl 2,4-dihydroxybenzoate (112 g), allyl bromide (78.6 g), potassium carbonate (92 g) and sodium iodide (1 g) were heated under reflux in butanone (1120 ml) for $2\frac{1}{2}$ hours. The mixture was cooled and filtered and the filtrate evaporated to dryness. The residue was distilled under reduced pressure to give the title compound as an oil (114.5 g) with b.p. 92° at 8×10^{-2} torr.

Preparation 22,4-Dihydroxy-3-(2-propenyl)benzoic acid, methyl ester

The compound of Preparation 1 (107.7 g) was heated at 200° in a nitrogen atmosphere for $2\frac{1}{2}$ hours. The oil was distilled under reduced pressure to give the title ester (89.5 g) as white crystals with b.p. 110° at 4×10^{-2} torr and m.p. $56-58^\circ$.

Preparation 32,4-Dihydroxy-3-propylbenzoic acid, methyl ester

The compound of Preparation 2 (72 g) was hydrogenated at atmospheric pressure in ethanol (1050 ml) using 10% palladium oxide on charcoal (5 g) as catalyst. The mixture was filtered, and the filtrate evaporated to dryness and the residue distilled under reduced pressure to give the title ester (68.9 g) b.p. 118° at 7×10^{-2} torr, m.p. $59-61^\circ$.

Preparation 4

(a) 1-[4-(4-Bromomethyl)phenylmethoxy-2-hydroxy-3-propylphenyl]ethanone

1-(2,4-Dihydroxy-3-propylphenyl)ethanone (5 g), 1,4-bis(bromomethyl)benzene (13.6 g) and potassium carbonate (7.5 g) were heated under reflux in butanone (100 ml) for 2 hours. The mixture was cooled, acidified with 2N hydrochloric acid and extracted with ether (50 ml). The organic phase was washed with ~

dried and evaporated to dryness. The residue was partially purified by chromatography on silica using petroleum ether as eluent to remove the excess of reagent and ethyl acetate as eluent to remove the crude product. The crude product was purified further by chromatography on silica using a mixture of petroleum ether (b.p. 60-80°) and dichloromethane (3:7) as the eluent to give the title compound (3.3 g) with m.p. 97-98°.

5 10 (b) 1-[4-(4-Chloro-2-butynyloxy)-2-hydroxy-3-propylphenyl] ethanone, m.p. 57-58° (from petroleum ether (b.p. 60 - 80°)) was prepared by a similar procedure from 1-(2,4-dihydroxy-3-propylphenyl)ethanone and 1,4-dichloro-2-butyne.

15 15 Preparation 5

1-[2-Hydroxy-4-(3-iodopropoxy)-3-propylphenyl]ethanone

1-[4-(3-Chloropropoxy)-2-hydroxy-3-propylphenyl] ethanone (20 g) and sodium iodide (22 g) were heated under reflux in butanone (400 ml) for 68 hours. The mixture was filtered, diluted with ether (200 ml) and washed with water and saturated brine. The organic phase was dried and evaporated to give an oil which was dissolved in petroleum ether. The solution was filtered and evaporated to dryness to give a solid which was recrystallised from aqueous isopropanol to give the title iodide (24.1 g) with m.p. 53-54°.

20 25 30 Preparation 6

(a) 3-[3-(3-Iodopropoxy)phenyl]-2-propenoic acid, methyl ester

35 3-(3-Hydroxyphenyl)-2-propenoic acid, methyl ester (15 g), 1-bromo-3-chloropropane (13.2 g) and potassium carbonate (15 g) were heated under reflux in butanone (150 ml) for 24 hours. The mixture was cooled and filtered and the filtrate heated under reflux with sodium iodide (19 g) for 7 hours. The mixture was cooled and

filtered and the filtrate diluted with ethyl acetate (200 ml) and washed with water, dried and evaporated. The residual oil was purified by chromatography on silica using a mixture of petroleum ether and ethyl acetate (3:1) as eluent. The major product was crystallised from petroleum ether (b.p. 60-80°) to give the title iodide (26 g) with m.p. 41-42°.

(b) 3-[3-(5-Iodopentyloxy)phenyl]-2-propenoic acid, methyl ester, b.p. 150° at 1×10^{-2} torr. was prepared by a similar procedure from 3-(3-hydroxyphenyl)-2-propenoic acid, methyl ester and 1,5-dibromopentane.

Preparation 7

(a) 1-[2-Hydroxy-4-(4-iodobutoxy)-3-propylphenyl]ethanone

A mixture of 1-(2,4-dihydroxy-3-propylphenyl)-ethanone (5 g), 1,4-dibromobutane (12 g), potassium carbonate (18 g) and butanone (100 ml) was heated under reflux for 5 hours. The cooled mixture was acidified with 2N hydrochloric acid and extracted with ether. The organic phase was washed with 2N sodium hydroxide solution, dried and concentrated. The residual crude bromide was dissolved in acetone (150 ml) and heated under reflux for 1 hour with sodium iodide (20 g). The cooled mixture was diluted with ether (200 ml), filtered and the filtrate evaporated to dryness. The residue was purified by chromatography on silica using a mixture of petroleum ether and ethyl acetate (4:1) as the eluent to give the title compound as a viscous oil (6.2 g).

(b) 1-[2-Hydroxy-4-(2-iodoethoxy)-3-propylphenyl]ethanone (m.p. 68-70°, from petroleum ether) was prepared by a similar procedure from 1-(2,4-dihydroxy-3-propylphenyl)ethanone and 1-bromo-2-chloroethane.

Preparation 8

1-(2,4-Dihydroxy-3,5-dipropylphenyl)ethanone
1-[2,4-Dihydroxy-3,5-di(2-propenyl)phenyl]ethanone
35 (2.1 g) was hydrogenated in ethanol (50 ml) using 10% palladium oxide on charcoal (0.1 g) as

mixture was filtered and the filtrate was evaporated to dryness and the residue recrystallised from toluene to give the title compound (1.8 g) with m.p. 98-99°.

Preparation 9

5 3-[2-Bromo-5-hydroxyphenyl]-2-propenoic acid, methyl ester

Bromine (1.3 ml) in methanol (40 ml) was added dropwise to a boiling solution of 3-(3-hydroxyphenyl)-2-propenoic acid (4 g) in methanol (40 ml) illuminated 10 with a 100 watt lamp. The addition was completed in 15 min. and the cooled solution was evaporated to dryness. The residue was crystallised from cyclohexane to give the title compound (2.9 g) with m.p. 128-30°.

Preparation 10

15 1-[2-Hydroxy-4-(3-hydroxypropoxy)-3-propylphenyl]-ethanone

1-(2,4-Dihydroxy-3-propylphenyl)ethanone (100 g), chloropropanol (48.7 g), potassium carbonate (141 g) and sodium iodide (5 g) were heated under reflux in 20 butanone (500 ml) for 76 h. The mixture was filtered and the filtrate diluted with ethyl acetate (1L). The solution was washed with 2N sodium hydroxide solution (3 x 250 ml) and 10% sodium thiosulphate solution (3 x 500 ml), dried and evaporated to give the crude title compound as an oil (109 g).

Preparation 11

1-[2-Hydroxy-4-[3-[[(4-methylphenyl)sulphonyl]oxy]-propoxy]-3-propylphenyl]ethanone

The compound of Preparation 10 (39 g), pyridine 30 (50 ml) and 4-toluenesulphonyl chloride (30 g) were stirred in dry ether (250 ml) for 16 h. The mixture was diluted with ethyl acetate (600 ml) and washed with water (2 x 500 ml), 8% sodium bicarbonate solution (500 ml), and 2N hydrochloric acid (2 x 500 ml), dried 35 and evaporated to dryness. The residue was triturated

with petroleum ether and recrystallised from a mixture of ethyl acetate and petroleum ether to give the title compound (38 g) with m.p. 88°.

Preparation 12

5 1-[4-(2-Butenyoxy)-2-hydroxyphenyl]ethanone

3-Chloro-1-butene (20 g) and sodium iodide (34 g) were heated under reflux in butanone (200 ml) for 25 h. The mixture was filtered and the filtrate heated under reflux with 1-(2,4-dihydroxyphenyl)ethanone (33.6 g) 10 and potassium carbonate (63 g) for 4 days. The cooled reaction mixture was filtered and the filtrate evaporated to dryness. The residue was extracted with petroleum ether (500 ml) and the solution evaporated to give an oil which was fractionally distilled at 15 162 - 175° at 0.1 torr. The resulting oil was purified by chromatography on silica using a mixture of petroleum ether and ethyl acetate (6:1) as the eluent. The fractions containing the component which had an Rf of 0.6 on t.l.c. (silica; petroleum ether : ethyl acetate 20 4:1) were collected and evaporated to dryness to give the title compound (20.1 g) as an oil.

Preparation 13

1-[2,4-Dihydroxy-3-[1-methyl-2-propenyl]phenyl]ethanone

The compound of Preparation 12 (1 g) was heated at 25 180 - 190° for 6 h under nitrogen. The solid which sublimed was collected and purified by chromatography on silica using a mixture of petroleum ether and ethyl acetate (5:1) as the eluent to give the title compound (0.4 g) with m.p. 146 - 147°.

30 Preparation 14

1-[2,4-Dihydroxy-3-(1-methylpropyl)phenyl]ethanone

The compound of Preparation 13 (0.4 g) was hydrogenated in ethanol (70 ml) using 5% palladium on charcoal as the catalyst. The mixture was filtered and the filtrate evaporated to dryness to give the title compound.

with m.p. 174 - 175°.

Preparation 15

3-[4-Acetyl-3-hydroxyphenyl]-2-propenoic acid, methyl ester

5 Aluminium chloride (14.97 g) was added to a mixture of 3-[3-hydroxyphenyl]-2-propenoic acid, methyl ester (10 g) and acetyl chloride (8 ml) in 1,2-dichloroethane (150 ml) at 0°. The mixture was stirred at 23° for 2 h and heated under reflux for 168 h. The mixture
10 was cooled, diluted with water and extracted with ethyl acetate. The extracts were dried and evaporated to dryness to give an oil which crystallised on the addition of petroleum ether. The solid was heated under reflux in a mixture of ethanol (50 ml) and 2N sodium hydroxide
15 (250 ml) for 1 h. The mixture was acidified with 2N hydrochloric acid and extracted with ethyl acetate. The extracts were dried and evaporated and the residue recrystallised from toluene to give the crude acid.

The crude acid was heated under reflux in
20 methanol (200 ml) containing concentrated sulphuric acid (1 ml) for 2 h. The mixture was concentrated to 50 ml, 8% sodium bicarbonate solution added and extracted with ethyl acetate. The extracts were dried and evaporated and the residue recrystallised twice
25 from cyclohexane to give the title ester (0.66 g) with m.p. 108 - 110°.

Preparation 16

2-Hydroxy-4-(5-hydroxypropoxy)benzoic acid, methyl ester

2,4-Dihydroxybenzoic acid, methyl ester (70g)
bromopropanol (58g) and potassium carbonate (57.5g)
5 were heated under reflux in butanone (1l) for 28h.
The mixture was filtered, the filtrate was evaporated
and the residue dissolved in ethyl acetate (500 ml).
The solution was washed with 8% sodium bicarbonate
solution, water and saturated brine, dried and
10 evaporated. The residual crude alcohol was recrystallised
from cyclohexane to give the title compound (56.6g),
with m.p. 76-77°.

Preparation 17

2-Hydroxy-4-[3-[[(4-methylphenyl)sulphonyl]oxy]propoxy]
15 benzoic acid, methyl ester

The compound of Preparation 16 (100g), pyridine
(70 ml) and 4-toluenesulphonyl chloride (104g) were
stirred in ether (1500 ml) in an ice bath for 2h and then
at room temperature for 58h. The reaction mixture was
20 filtered and the filtrate was washed with 2N hydrochloric
acid, water and sodium bicarbonate, dried and evaporated
to give an oil which solidified when triturated with
ether. The crystals were washed with dilute hydrochloric
acid, air dried and recrystallised from a mixture of
25 ethanol and water to give the title compound (102g), with
m.p. 111-112.5°.

Preparation 18

2,4-Dihydroxy-3-propylbenzoic acid

The compound of Preparation 3 (2g) was heated
30 at 100° for 1h in 2N sodium hydroxide (10 ml). The
solution was cooled and acidified and the precipitate
filtered off and recrystallised from water to give the
title acid (0.6g), with m.p. 176-178°.

Preparation 19

35 2-Propylbenzene-1,3-diol

The compound of Preparation 18 (130g) was heated

under nitrogen at 190° for 1.5h. The mixture was cooled, dissolved in ether and the solution was washed with 4% sodium bicarbonate solution dried and evaporated. The residue was recrystallised from cyclo-

5 hexane to give the title diol (59.6g), with m.p. 97-99°.

Preparation 20

a) (2,4-Dihydroxy-3-propylphenyl)phenylmethanone

The compound of Preparation 19 (2g), anhydrous 10 zinc chloride (4g) and benzoic acid (7.3g) were heated at 150° for 2.5h. The reaction mixture was cooled and dissolved in a mixture of 2N hydrochloric acid and ethyl acetate. The layers were separated and the organic phase washed with 4% sodium bicarbonate (3 x 50 ml), dried 15 and evaporated. The residue (3.5g) was purified by chromatography on silica (150g) using a mixture of petroleum ether and ethyl acetate (4:1) as the eluent and recrystallised from cyclohexane to give the title ketone (2.1g), with m.p. 152-153°.

20 The following compounds were prepared by a similar procedure from the compound of Preparation 19 and the appropriate acid.

b) 1-(2,4-Dihydroxy-3-propylphenyl)-1-propanone

m.p. 104-106° from propionic acid

25 c) 1-(2,4-Dihydroxy-3-propylphenyl)-2-phenylethanone,
m.p. 128-130°, from phenylacetic acid.

Preparation 21

1-[4-(9-Bromononyloxy)-2-hydroxy-3-propylphenyl]ethanone

The title compound was prepared as an oil from 30 1-(2,4-dihydroxy-3-propylphenyl)ethanone and 1,9-di-bromononane by a similar procedure to Preparation 4.

Preparation 22

1-[4-(2-Heptynyloxy)-2-hydroxyphenyl]ethanone

The title compound was prepared as an oil from 35 1-(2,4-dihydroxyphenyl) ethanone and 1-bromo-2-heptene by a similar procedure to Preparation 12.

Preparation 231-[2,4-Dihydroxy-3-(1-methylhexyl)phenyl]ethanone

The compound of Preparation 22 (0.94g) was heated at 190° for 3h under nitrogen. The mixture was 5 purified by chromatography on silica using a mixture of petroleum ether and ethyl acetate (3:1) as the eluent to give a solid (0.41g). The crude alkene was hydrogenated in ethanol (30 ml) using 10% palladium oxide on charcoal as the catalyst. The mixture was filtered and the 10 filtrate was evaporated to dryness to give a solid. The solid was recrystallised from a mixture of ethanol and water to give the title compound (0.22g) with m.p. 78-81°.

Preparation 243-[3-Acetoxyphenyl]-2,3-dibromopropanoic acid, methyl ester

15 Bromine (3.7 ml) in carbon tetrachloride (150 ml) was added dropwise to a solution of 3-[3-acetoxyphenyl]-2-propenoic acid, methyl ester (15g) in carbon tetrachloride (150 ml) illuminated with a 60 watt lamp. The addition was completed in 2.5h and the solution was 20 stirred for a further 2.5h. The solution was evaporated to dryness and the residual solid was recrystallised from a mixture of methanol and water to give the title compound (19.5g), with m.p. 84-86°.

Preparation 252-Bromo-3-(3-hydroxyphenyl)-2-propenoic acid

The compound of Preparation 24 (11.4g) in dioxan (150 ml) was added to a solution of potassium hydroxide (15g) in water (75 ml) and dioxan (75 ml). The solution was stirred for 20h. The product mixture was acidified 30 with 2N hydrochloric acid, and extracted with ethyl acetate (2 x 500 ml). The combined organic extracts were evaporated to give an oil. The oil was crystallised from water to give the title acid (2.52g) with m.p. 178-180°.

Preparation 26

2-Bromo-5-(5-hydroxyphenyl)-2-propenoic acid, methyl ester

Acetyl chloride (2 ml) was added cautiously to ice-cold methanol (40 ml). The compound of Preparation 5 25 (2g) was added and the solution was heated under reflux for 5h, cooled and evaporated to dryness. The residual oil was dissolved in ethyl acetate and the solution was washed consecutively with 8% sodium bicarbonate solution and water, dried and evaporated.

10 The residual solid was recrystallised from a mixture of methanol and water to give the title ester (1.39g), with m.p. 97-99°.

Preparation 27

5-Bromo-2-hydroxy-4-[3-[[(4-methylphenyl)sulphonyl]oxy]propoxy]benzoic acid, methyl ester

A solution of bromine (0.1 ml) in chloroform (10 ml) was added to a solution of the compound of Preparation 17 (1g) in chloroform (25 ml). The reaction mixture was stirred for 5h and diluted with ether (200 ml). The solution was washed consecutively with 8% sodium bicarbonate solution, water and saturated brine dried and evaporated to dryness to give a white solid. The solid was recrystallised from a mixture of ethyl acetate and petroleum ether to give the title compound (1g), with 25 m.p. 141-142°.

Preparation 28

2-Hydroxy-4-[3-[[(4-methylphenyl)sulphonyl]oxy]propoxy]-5-nitrobenzoic acid, methyl ester

Nitric acid (1 ml) was added dropwise to a 30 solution of the compound of Preparation 17 (1.5g) in chloroform (20 ml). The reaction mixture was stirred for 16h and then diluted with ethyl acetate (200 ml). The solution was washed consecutively with 8% sodium bicarbonate solution, water and saturated brine, dried 35 and evaporated to give a red solid. The solid was re-

crystallised from a mixture of ethyl acetate and petroleum ether to give the title compound (0.55g), with m.p. 143-145°.

Preparation 29

5 2-Hydroxy-4-[3-[methylsulphonyl]oxy]propoxy]benzoic acid, methyl ester

Methanesulphonyl chloride (1.26g) in dichloromethane (10 ml) was added dropwise over 15 min. to a solution of the compound of Preparation 16 (2.52g) and 10 triethylamine (1.5g) in dichloromethane (30 ml) at 0 to -5°. The mixture was stirred for a further 15 min. at 0°, then washed successively with water, 2N hydrochloric acid, 8% sodium bicarbonate solution and saturated brine, dried and evaporated. The residual solid was recrystallised 15 from methanol to give the title mesylate (2.2g), with m.p. 87-89°.

Preparation 30

2,4-Dihydroxybenzoic acid, phenylmethyl ester

2,4-Dihydroxybenzoic acid was dissolved in a 20 solution of potassium carbonate (4.35g) in water (50 ml) heated on a steam bath. The solution was evaporated to dryness and the residual solid washed well with acetone and dried to give the potassium salt (12.44g). The potassium salt (12.44g), benzylchloride (7.55 ml; 8.3g) 25 and triethylbenzylammonium chloride (0.93g) were heated at 100° in dimethylformamide (120 ml) for 24h. Water (120 ml) was added and the mixture was acidified and extracted with ether. The extracts were washed with water and 2% sodium bicarbonate solution, dried and 30 evaporated. The residual oil was crystallised from cyclohexane to give the title ester (10.84g), with m.p. 93-94°.

Preparation 31

2-Hydroxy-4-[3-hydroxypropoxy]benzoic acid, phenylmethyl 35 ester

The compound of Preparation 30 (10.5g), 3-bromo-1-

propanol (3.9 ml; 5.99g) and potassium carbonate (5.94g) were heated under reflux in butanone (100 ml) for 24h. Water (100 ml) and ethyl acetate (100 ml) were added and the organic phase was separated and washed consecutively with water, 1N sodium carbonate and saturated brine and dried. The solution was evaporated to dryness and the residue (12.1g) purified by chromatography on silica (600g), using a mixture of petroleum ether and ethyl acetate (2:1) as the eluent. The fractions containing the major component were combined and evaporated to dryness to give the title alcohol as a white solid (5.7g), with m.p. 65-66°.

Preparation 32

2-Hydroxy-4-[3-[methylsulphonyloxy]propoxy]benzoic acid, phenylmethyl ester

A solution of methanesulphonyl chloride (0.56 ml; 0.83g) in dichloromethane (10 ml) was added dropwise over 15 min to a solution of the compound of Preparation 31 (2g) and triethylamine (1.38 ml; 1.0g) in dichloromethane (50 ml) cooled in ice. The solution was stirred at room temperature for 15 min and washed with 1N hydrochloric acid, 1% sodium bicarbonate and saturated brine, dried and evaporated to dryness. The residue or solid was recrystallised from methanol to give the title mesylate (2.23 g), with m.p. 84-85°.

Preparation 33

4-[5-[4-Acetyl-3-hydroxy-2-(2-propenyl)phenoxy]propoxy]2-hydroxybenzoic acid, phenylmethyl ester

1-[2,4-Dihydroxy-3-(2-propenyl)phenyl]ethanone (1.01g), the compound of Preparation 32 (2.0g) and potassium carbonate (0.73g) were heated under reflux in butanone (50 ml) for 24h. The mixture was diluted with water (50 ml), the layers were separated and the aqueous phase was extracted with ethyl acetate. The organic phases were washed with saturated brine, dried and evaporated.

The residual semi-solid was extracted with hot cyclohexane (200 ml) and the solution was evaporated to dryness. The residue was recrystallised three times from ethanol to give the title ester (1.28 g) with m.p. 111-112°.

5 Preparation 54

1-[2-Hydroxy-4-[3-[methylsulphonyl]oxy]propoxy]-3-(2-propenyl)phenylethanone

1-[2,4-Dihydroxy-3-(2-propenyl)phenyl]ethanone (4.65g), 3-bromo-1-propanol (2.2 ml; 3.38g) and potassium carbonate (3.34g) were heated under reflux in butanone (50 ml) for 16h. The mixture was cooled, diluted with water (50 ml) and acidified with 2N hydrochloric acid. The layers were separated and the aqueous phase was extracted with ethyl acetate. The combined organic phases were washed with saturated brine, dried and evaporated to give the crude intermediate alcohol as an oil (5.8g). A solution of methanesulphonyl chloride (1.7ml; 2.52g) in dichloromethane (30 ml) was added dropwise over 15 min to a solution of the crude alcohol (5.0g) and triethylamine (4.2 ml; 3.05g) in dichloromethane (90 ml) cooled in ice. The solution was stirred at room temperature for 30 min and washed with 1N hydrochloric acid, 4% sodium bicarbonate and saturated brine, dried and evaporated. The residual oil was crystallised from methanol to give the title mesylate (5.03g), with m.p. 81-82°.

Preparation 55

1-[2-Hydroxy-4-[3-(3-hydroxyphenoxy)propoxy]-3-propylphenyl]ethanone

30 The compound of Example 8 (4g) was heated at 200° for 1h. The cooled melt was dissolved in ethyl acetate (200 ml) and the solution was washed with 4% sodium bicarbonate solution, dried and evaporated. The residual oil was crystallised from cyclohexane to give the title phenol (1.7g), with m.p. 87-89°.

Preparation 36(a) 2-Methoxy-4-[5-[[(4-methylphenyl)sulphonyl]oxy]propoxy]benzoic acid, methyl ester

The compound of Preparation 17 (1g) was added to
5 0.1 N sodium hydroxide solution (26.6 ml) and the mixture was evaporated to dryness. The residual solid was stirred at 25° in a mixture of dimethyl sulphate (8.75 ml), triethylbenzylammonium chloride (0.1g) and butanone (50 ml) for 1.5h. The mixture
10 was acidified with 2 N hydrochloric acid and extracted with ether (3 x 25 ml). The combined organic extracts were washed with water and saturated brine, dried and evaporated to dryness. The residue was heated on a steam bath with 8% sodium bicarbonate solution (150 ml) and the cooled mixture was extracted with ethyl acetate. The organic extracts were dried and evaporated to give the title compound (0.51g) as an oil, with λ_{max} .
15 255 (ε 14,500).

Preparation 3720 4-[3-[4-Acetyl-3-hydroxy-2-(2-propenyl)phenoxy]-propoxy]-2-hydroxybenzoic acid, phenylmethyl ester

The compound of Preparation 34 (2.75g), the compound of Preparation 30 (2.05g) and potassium carbonate (1.16g) were heated under reflux in butanone (70 ml)
25 for 24h. Water (70 ml) was added, the layers separated and the aqueous layer was extracted with ethyl acetate. The organic phases were washed with saturated brine, dried and evaporated. The residue was recrystallised from ethanol to give the title ester (3.22g), with
30 m.p. 111-112°.

EXAMPLE 1(a) 3-[3-(4-Acetyl-3-hydroxy-2-propylphenoxy)propoxy]benzoic acid

Sodium hydride (oil free; 0.18 g) was added to a
5 solution of 3-hydroxybenzoic acid, methyl ester (1.12 g)
dissolved in dry dimethylformamide (25 ml). The mixture
was stirred at 25° for 15 min. and sodium iodide (0.5 g)
and 1-[4-(3-chloropropoxy)-2-hydroxy-3-propylphenyl]
ethanone (1.0 g) added. The mixture was heated at 110°
10 for 3 hours cooled and evaporated to dryness. The
residual oil was triturated with water and purified
by chromatography on silica using a mixture of ethyl
acetate and petroleum ether (1:2) as the eluent to give
the methyl ester of the title compound (0.7 g).

15 The ester was dissolved in N/3 ethanolic sodium
hydroxide (30 ml) and the solution heated under reflux
for 20 minutes. The solvent was removed under reduced
pressure and the residue washed with ethyl acetate and
dissolved in water. The solution was acidified with
20 2N hydrochloric acid and the solid filtered off and
recrystallised from a mixture of ethanol and water
to give the title acid (0.5 g) with m.p. 138-139°.

The following compounds were prepared by a
similar procedure from 1-[4-(3-chloropropoxy)-2-hydroxy-
25 3-propylphenyl]ethanone and the appropriate ester:-

(b) 3-[4-[3-(4-Acetyl-3-hydroxy-2-propylphenoxy)propoxy]
phenyl]-2-propenoic acid, m.p. 176-178° (from aqueous
acetone) (methyl ester had m.p. 135-137° (from aqueous
ethanol)); from 3-(4-hydroxyphenyl)-2-propenoic acid,
50 methyl ester.

(c) 3-[3-(4-Acetyl-3-hydroxy-2-propylphenoxy)propoxy]
benzeneacetic acid, m.p. 81.5-82° (from petroleum ether);
from 3-hydroxybenzeneacetic acid, ethyl ester.

(d) 4-[3-(4-Acetyl-3-hydroxy-2-propylphenoxy)propoxy]
35 benzoic acid, m.p. 186-187.5° (from aqueous acetone);
from 4-hydroxybenzoic acid, methyl ester.

(e) 5-[3-(4-Acetyl-3-hydroxy-2-propylphenoxy)propoxy]benzenepropanoic acid, m.p. 71-72° (from a mixture of dilute hydrochloric acid and methanol); from 3-hydroxybenzenepropanoic acid, methyl ester.

5 (f) 2-[3-[3-(4-Acetyl-3-hydroxy-2-propylphenyl)propoxy]phenoxy]acetic acid, m.p. 117-118° (from aqueous ethanol); from 3-hydroxyphenoxyacetic acid, methyl ester.

(g) 2-[4-[3-(4-Acetyl-3-hydroxy-2-propylphenyl)propoxy]phenoxy]acetic acid, m.p. 123-124° (from aqueous ethanol);

10 from 4-hydroxyphenoxyacetic acid, ethyl ester.

EXAMPLE 2

(a) 3-[3-[3-(4-Acetyl-3-hydroxy-2-propylphenoxy)propoxy]phenyl]-2-propenoic acid

15 A mixture of 3-(3-hydroxyphenyl)-2-propenoic acid, methyl ester (4.9 g), the compound of Preparation 5 (10 g) and potassium carbonate (4 g) in butanone (250 ml) was heated under reflux for 24 hours. The mixture was reduced to dryness and the residue extracted with ethyl acetate. The extracts were evaporated to give an oil which was

20 crystallised from a mixture of ethanol and water to give the methyl ester of the title compound (8.9 g) with m.p. 88-89°.

A mixture of the ester (7.8 g) lithium hydroxide monohydrate (4 g), tetrahydrofuran (30 ml) and water (30 ml) was stirred at 25° for 5 hours and diluted with water (200 ml). The aqueous solution was washed with ether (3 x 75 ml) and acidified with 2N hydrochloric acid. The precipitate was filtered off and recrystallised from ethanol to give the title acid (5.13 g) with m.p. 30 151-153°.

The following compounds were prepared by a similar procedure:

(b) 5-[3-(4-Acetyl-3-hydroxy-2-propylphenoxy)propoxy]carboxylic acid, m.p. 224-225° (from aqueous 100 ml) from 5-hydroxy-1,3-benzenedicarboxylic acid, methyl ester and the compound of Preparation 5.

(c) 4-[3-(4-Acetyl-3-hydroxy-2-propylphenoxy)propoxy]-2-hydroxy-3-propylbenzoic acid, m.p. 170-172° (from aqueous ethanol); from the compound of Preparation 5 and the compound of Preparation 3.

5 (d) 3-[3-[4-(4-Acetyl-3-hydroxy-2-propylphenoxy)methyl-phenyl]methoxyphenyl]-2-propenoic acid, m.p. 163-164° (from ethanol) (methyl ester had m.p. 110-111° (from a mixture of ethyl acetate and petroleum ether)); from 3-(3-hydroxyphenyl)-2-propenoic acid, methyl ester and the compound of Preparation 4a.

10 (e) 3-[3-[4-(4-Acetyl-3-hydroxy-2-propylphenoxy)butoxy]-phenyl]-2-propenoic acid, m.p. 115-117° (from a mixture of ethyl acetate and petroleum ether; from the compound of Preparation 7a and 3-(3-hydroxyphenyl)-2-propenoic acid, methyl ester.

15 (f) 3-[3-[2-(4-Acetyl-3-hydroxy-2-propylphenoxy)ethoxy]-phenyl]-2-propenoic acid, m.p. 120-121° (from a mixture of ethyl acetate and petroleum ether); from the compound of Preparation 7b and 3-(3-hydroxyphenyl)-2-propenoic acid, methyl ester.

20 (g) 3-[3-[4-(4-Acetyl-3-hydroxy-2-propylphenoxy)-2-butynyloxy]phenyl]-2-propenoic acid, m.p. 146-147° (from a mixture of ethyl acetate and petroleum ether) (methyl ester had m.p. 83-84° (from a mixture of petroleum ether and ethyl acetate)); from 3-(3-hydroxyphenyl)-2-propenoic acid, methyl ester and the compound of Preparation 4b.

25 (h) 3-[2-[3-(4-Acetyl-3-hydroxy-2-propylphenoxy)-propoxy]phenyl]-2-propenoic acid, m.p. 145-147° (from aqueous ethanol) (methyl ester had m.p. 78-80°) from aqueous ethanol); from the compound of Preparation 5 and 3-(2-hydroxyphenol)-2-propenoic acid, methyl ester.

30 (i) 3-[5-[3-(4-Acetyl-3-hydroxy-2-propylphenoxy)propoxy]-2-bromophenyl]-2-propenoic acid, m.p. 168-169° (from aqueous methanol); from the compound of Preparation 5 and the compound of Preparation 9.

EXAMPLE 33-[3-[3-(4-Acetyl-3-hydroxy-2-propylphenoxy)propoxy]phenyl]-N-1H-tetrazole-5-yl-2-propenamide

The compound of Example 2 (0.5 g) and N,N'-carbon-
5 yldiimidazole (0.45 g) were stirred at 25° in a mixture
of dry tetrahydrofuran (15 ml) and dry dimethylformamide
(1 ml) for 17 hours. A solution of 5-aminotetrazole
(0.4 g) in dimethylformamide (10 ml) was added and the
mixture stirred at 25° for 4 hours and at 90° for 2½ hours.
10 The mixture was cooled and diluted with water (100 ml)
and the precipitate filtered off, washed with ether and
recrystallised from a mixture of dimethylformamide and
water to give the title amide (0.29 g) with m.p. 234-236°.

15 EXAMPLE 4(a) 3-[3-[3-(4-Acetyl-3-hydroxy-2-(2-propenyl)phenoxy]propoxy]phenyl]-2-propenoic acid

1-[2,4-Dihydroxy-3-(2-propenyl)phenyl]ethanone
(1.5 g), the compound of Preparation 6a (2.7 g) and
20 potassium carbonate (2.5 g) were heated under reflux in
butanone (25 ml) for 8 hours. The mixture was evaporated
to dryness and the residue dissolved in a mixture of 2N
hydrochloric acid and ethyl acetate. The organic layer
was washed with 2N sodium carbonate solution, dried and
25 evaporated to dryness. The residue was recrystallised
from ethanol to give the methyl ester of the title compound
(2.6 g) with m.p. 89-90°.

A mixture of the ester (1.5 g), lithium hydroxide
monohydrate (0.8 g), water (15 ml) and tetrahydrofuran
30 (15 ml) was stirred at room temperature for 20 hours.
The mixture was washed with ether (2 x 10 ml) and the
aqueous layer acidified. The precipitate was filtered
off and recrystallised from ethanol to give the title
acid (1.2 th m.p. 127.5-128.5°).

..-1-Acetyl-3-hydroxy-2-propylphenoxy)pentyl-
.]phenyl]-2-propenoic acid, m.p. 126-127°, (from

aqueous ethanol); from 1-[2,4-dihydroxy-3-propylphenyl] ethanone and the compound of Preparation 6b.

(c) 3-[3-[3-(4-Acetyl-3-hydroxy-2-methylphenoxy)propoxy]phenyl]-2-propenoic acid, m.p. 157.5-159° (from ethanol)
5 (methyl ester had m.p. 87-89° (from ethanol)); from 1-(2,4-dihydroxy-3-methylphenyl)ethanone and the compound of Preparation 6a.

(d) 3-[3-[3-(4-Acetyl-3-hydroxy-2,6-dipropylphenoxy)propoxy]phenyl]-2-propenoic acid, m.p. 123.5-125° (from
10 aqueous ethanol); from the compound of Preparation 6a and the compound of Preparation 8.

(e) 3-[3-[3-[4-Acetyl-3-hydroxy-2-(1-methylpropyl)phenoxy]propoxy]phenyl]-2-propenoic acid, m.p. 126.5-129°, (from aqueous ethanol); from the compound of Preparation 14 and
15 the compound of Preparation 6a.

EXAMPLE 5

3-[3-(4-Acetyl-3-hydroxy-2-propylphenoxy)propoxy]benzene propanoic acid

The compound of Example 2 (0.37 g) was hydrogenated
20 in methanol (25 ml) using 10% palladium oxide on charcoal as catalyst. The mixture was filtered and the filtrate evaporated to dryness to give a brown oil which was purified by chromatography on silica (15 g) using a mixture of petroleum ether and ethyl acetate (2:1) as the eluent. The product was crystallised from a mixture of methanol and 10% aqueous acetic acid to give the title
25 acid (0.09 g) with m.p. 72-73°.

EXAMPLE 6

3-[3-(4-Acetyl-3-hydroxy-2-propylphenoxy)methoxy]phenyl]-2-propenoic acid

A mixture of 1-(2,4-dihydroxy-3-propylphenyl)ethanone (7 g), 3-(3-hydroxyphenyl)-2-propenoic acid, methyl ester (6.4 g), dibromomethane (30 g) and potassium carbonate (60 g) was heated under reflux in butanone (200 ml) for 18 hours. The cooled mixture was filtered,

diluted with ether (200 ml) and washed with water and 2N sodium hydroxide solution. The solution was dried and evaporated to give an oil which was purified by chromatography on silica using dichloromethane as the eluent to give the methyl ester of the title compound (3.2 g) which had m.p. 87-87.5° after recrystallisation from petroleum ether.

A mixture of the ester (1.5 g), lithium hydroxide monohydrate (1 g), tetrahydrofuran (30 ml) and water (30 ml) was stirred at 25° for 4 hours. The reaction mixture was washed with ether, acidified with 2N hydrochloric acid and extracted with ethyl acetate. The extracts were dried and evaporated and the residue recrystallised from a mixture of petroleum ether and ethyl acetate to give the title acid with m.p. 174-175°.

EXAMPLE 7

3-[3-[4-(4-Acetyl-3-hydroxy-2-propylphenoxy)-2-butenyloxy]phenyl]-2-propenoic acid

The compound of Example 2g (0.95 g) was hydrogenated in pyridine (20 ml) using 5% palladium on barium sulphate as catalyst. The catalyst was filtered off after the theoretical volume of hydrogen had been absorbed and the filtrate evaporated to dryness. The residue was recrystallised from a mixture of ethyl acetate and petroleum ether (b.p. 60-80°) to give the title acid (0.72 g) with m.p. 126-129°.

EXAMPLE 8

4-[3-(4-Acetyl-3-hydroxy-2-propylphenoxy)propoxy]-2-hydroxybenzoic acid

30 Methyl 2,4-dihydroxybenzoate (5 g), the compound
of Preparation 5 (10.8 g) and potassium carbonate (4.5 g)
were heated under reflux in butanone (700 ml) for 26 h.
31 The reaction mixture was filtered and the filtrate evaporated to
dryness. The residue was recrystallised from methanol
32 to give the methyl ester of the title compound (8.6 g).

with m.p. 95 - 96°.

The ester (1 g) and sodium hydroxide (0.48 g) were heated under reflux in a mixture of methanol (63 ml) and water (5 ml) for 14 h. The solution was 5 evaporated to dryness and the residue dissolved in water. The solution was acidified and extracted with ethyl acetate. The extracts were dried and evaporated and the residue recrystallised from a mixture of acetone and water to give the title compound (0.8 g) with m.p. 173 - 10 174°.

EXAMPLE 9

(a) 3-[5-[3-[4-Acetyl-3-hydroxy-2-propylphenoxy]propoxy]-2-nitrophenyl]-2-propenoic acid

3-[5-Hydroxy-2-nitrophenyl]-2-propenoic acid, 15 methyl ester (3 g), the compound of Preparation 11 (5.5 g) and potassium carbonate (3.75 g) were heated under reflux in butanone (150 ml) for 6 h. The mixture was cooled, acidified with 2N hydrochloric acid and extracted with ethyl acetate. The extracts were washed with 2N sodium 20 carbonate (2 x 200 ml) and water (2 x 200 ml), dried and evaporated to give the crude methyl ester of the title compound as an oil (6 g).

The crude ester (4.6 g) and lithium hydroxide monohydrate (2 g) were stirred in a mixture of water (40 ml) 25 and tetrahydrofuran (40 ml) for 6 h. The mixture was diluted with water (200 ml), washed with ether and the aqueous layer acidified and extracted with ethyl acetate. The extracts were dried and evaporated to dryness and the residue recrystallised from a mixture of ethyl acetate and 30 petroleum ether to give the title compound (3.2 g) with m.p. 158 - 160°.

The following compounds were prepared by a similar procedure:

(b) 3-[3-[3-[4-Acetyl-3-hydroxy-2-propylphenoxy]propoxy]-4-nitrophenyl]-2-propenoic acid, m.p. 191 - 194° (from 35 ethanol); from 3-[3-hydroxy-4-nitrophenyl]-2-propenoic acid,

methyl ester and the compound of Preparation 11.

(c) 3-[3-[3-[4-Acetyl-3-hydroxy-2-propylphenoxy]propoxy]-4-acetylphenyl]-2-propenoic acid, m.p. 200 - 202° (from aqueous ethanol); from the compound of Preparation 15 and 5 the compound of Preparation 11.

(d) 5-[3-[4-Acetyl-3-hydroxy-2-propylphenoxy]propoxy]-3-hydroxybenzoic acid, m.p. 170 - 172°; from methyl 3,5-dihydroxybenzoate and the compound of Preparation 11.

EXAMPLE 10

10 (a) 5-[2-[3-[3-[4-Acetyl-3-hydroxy-2-propylphenoxy]propoxy]-ethenyl]-1H-tetrazole hemihydrate

3-[3-Hydroxyphenyl]propenonitrile (2 g), the compound of Preparation 11 (5.56g) and potassium carbonate (3.78g) were heated under reflux in 15 butanone (70 ml) for 8 h. The mixture was acidified with hydrochloric acid and extracted with ethyl acetate. The extracts were dried and evaporated and the residue recrystallised from cyclohexane to give the intermediate nitrile (3.7 g) with m.p. 20 110 - 111°.

The nitrile (1g), ammonium chloride (0.14g) and sodium azide (0.18 g) were heated in dimethyl-formamide (25 ml) at 120° for 21 h. The mixture was cooled, diluted with water (200 ml) and 25 acidified with 2N hydrochloric acid. The mixture was extracted with ethyl acetate and the extracts dried and evaporated to dryness. The residue was heated at 100° with 5N hydrochloric acid for 0.75h. The mixture was cooled and the solid filtered off 30 and recrystallised from acetic acid to give the title compound (0.48 g) with m.p. 102 - 104°.

The following compound was prepared by a similar procedure.

(b) 5-[3-[3-[4-Acetyl-3-hydroxy-2-propylphenoxy]propoxy]-phenyl]-1H-tetrazole, m.p. 154-156° (from a mixture of water and ethanol); from 3-cyanophenol and the compound of Preparation 11 (the intermediate nitrile had m.p. 60 - 5 61° (from cyclohexane)).

EXAMPLE 11

a) 4-[3-(4-Acetyl-3-hydroxy-2-propylphenoxy)propoxy]-2-hydroxybenzoic acid

Methyl 2,4-dihydroxybenzoate (7.03 g), the compound 10 of Preparation 11 (17 g) and potassium carbonate (11.5 g) were heated under reflux in butanone (300 ml) for 20 h. The mixture was cooled, diluted with water (150 ml) and the layers separated. The aqueous phase was extracted with ethyl acetate and the combined organic phases dried and 15 evaporated to dryness. The residue was recrystallised from methanol to give the methyl ester of the title compound (13.56 g) with m.p. 95 - 96°.

The ester (13.5 g) and sodium hydroxide (4.5 g) 20 were heated under reflux in a mixture of methanol (780 ml) and water (65 ml) for 21 h. The mixture was acidified, the methanol distilled off under reduced pressure and the resulting suspension filtered. The solid was washed with water, dissolved in hot acetone (130 ml) and the solution diluted with water (80 ml). The crystals which 25 formed on cooling were filtered off and recrystallised from toluene to give the title compound (9.9 g) with m.p. 176 - 177°.

The following compounds were prepared by a similar procedure from the compound of Preparation 11 and the 30 appropriate ester:

b) 4-(3-[4-Acetyl-3-hydroxy-2-propylphenoxy]propoxy)-2-hydroxy-3-(2-propenyl)benzoic acid, m.p. 178-180° (from a mixture of ethanol and water) (methyl ester had m.p. 84-86° (from a mixture of ethanol and water)); from 35 the compound of Preparation 2.

c) 4-[3-(4-Acetyl-3-hydroxy-2-propylphenoxy)propoxy]-2-hydroxy-3-methyl-benzoic acid hemihydrate, m.p. 177-

179° (from a mixture of ethanol and water) (ethyl ester had m.p. 110-113°); from 2,4-dihydroxy-3-methylbenzoic acid, ethyl ester.

d) 3-[3-(4-Acetyl-3-hydroxy-2-propylphenoxy)propoxy]-
5 2-hydroxybenzoic acid, m.p. 172° (from a mixture of ethanol and water) (methyl ester had m.p. 93-96° (from a mixture of ethyl acetate and petroleum ether)); from 2,3-dihydroxybenzoic acid, methyl ester.
e) 5-[3-(4-Acetyl-3-hydroxy-2-propylphenoxy)propoxy]-2-
10 hydroxybenzoic acid, m.p. 155-156° (from a mixture of ethanol and water); from 2,5-dihydroxybenzoic acid, ethyl ester.

EXAMPLE 12

a) 4-[3-(4-Acetyl-3-hydroxy-2-propylphenoxy)propoxy]-
15 2-hydroxybenzoic acid
1-(2,4-Dihydroxy-3-propylphenyl)ethanone (3g), the compound of Preparation 17 (3.8g) and potassium carbonate (1.38g) were heated under reflux in butanone (300 ml) for 16h. The mixture was acidified with 2N hydrochloric acid and extracted with ethyl acetate. The extracts were washed consecutively with water, 8% sodium bicarbonate solution and saturated brine, dried and evaporated to give the crude methyl ester of the title compound (3.6g) as an oil.
20
25 The ester (3.6g) was heated under reflux in a mixture of ethanol (30 ml) and 2N sodium hydroxide (200 ml) for 5h. The mixture was acidified and extracted with ethyl acetate. The extracts were washed with water and saturated brine, dried and evaporated. The residue
30 was recrystallised once from a mixture of ethanol and water and once from toluene to give the title compound (1.8g), with m.p. 175-176°.

The f g compounds were prepared by a similar

35 d) 4-[3-(4-Acetyl-3-hydroxy-2-[(1-methylhexyl)phenoxy]oxy]-2-hydroxybenzoic acid, m.p. 106-108° (from a mixture of ethanol and water); from the compound of



Preparation 17 and the compound of Preparation 23.

c) 4-[3-(3-Hydroxy-4-(1-oxopropyl)-2-propylphenoxy]propanoic acid, m.p. 155-158° (from a mixture of ethanol and water) (methyl ester had m.p.

5 79-80° (from a mixture of ethanol and water)); from the compound of Preparation 17 and the compound of Preparation 20b.

d) 4-[3-[3-Hydroxy-4-phenylacetyl-2-propylphenoxy]propanoic acid, m.p. 167-169° (methyl ester had m.p. 102-103° (from ethanol)); from the compound of Preparation 17 and the compound of Preparation 20c.

e) 4-[3-[4-Benzoyl-3-hydroxy-2-propylphenoxy]propanoic acid, m.p. 91-92° (from toluene) (methyl ester had m.p. 117-118° (from ethanol)); from the compound of Preparation 17 and the compound of Preparation 20a.

Example 13

3-[3-[3-(4-Acetyl-3-hydroxy-2-propylphenoxy)propanoic acid]phenyl]-2-propenoic acid

The compound of Preparation 11 (1.62g) the compound of Preparation 26 (1.03g) and potassium carbonate (1.21g) were heated under reflux in butanone (120 ml) for 24h.

25 The mixture was cooled, filtered and the filtrate was evaporated to dryness. The resulting oil was purified by chromatography on silica using a mixture of petroleum ether and ethyl acetate (3:1) as the eluent to give the methyl ester of the title compound (1.1g), with m.p. 56-58°.

A mixture of the ester (0.91g), lithium hydroxide monohydrate (0.373g), tetrahydrofuran (20 ml) and water (20 ml) was stirred at room temperature for 6h, washed with ether (2 x 50 ml) and acidified with 2N hydrochloric acid. The mixture was extracted with ethyl acetate (2 x 50 ml). The extracts were dried and evaporated to give a solid which was recrystallised twice from a mixture of

ethyl acetate and petroleum ether to give the title acid (0.372g), with m.p. 153-156°.

Example 14

4-[3-(4-Acetyl-3-hydroxy-2-propylphenoxy)-2-hydroxypropoxy]-2-hydroxybenzoic acid

A mixture of 1-[2-hydroxy-4-(oxiranylmethoxy)-3-propylphenyl]ethanone (1g), 2,4-dihydroxybenzoic acid, methyl ester (0.672g) and benzyltrimethylammonium hydroxide (1 drop) in dimethylformamide (40 ml) was 10 heated under reflux for 6h. The mixture was reduced to dryness and the residue was dissolved in ethyl acetate. The solution was washed consecutively with water, 1N sodium hydroxide solution, water and saturated brine, dried and evaporated to give an oil. The oil was purified 15 by chromatography on silica using a mixture of petroleum ether and ethyl acetate (2:1) as the eluent. The fractions containing the component which had an Rf of 0.33 on t.l.c. (silica; petroleum ether:ethyl acetate 2:1) were collected and evaporated to dryness to give the methyl ester of the 20 title compound (0.52g), with m.p. 126-128°.

The ester (0.418g), sodium hydroxide (0.2g), methanol (30 ml) and water (2 ml) were heated under reflux for 24h. The methanol was removed under reduced pressure, the residual aqueous solution was acidified with 25 2N hydrochloric acid and extracted with ethyl acetate (2 x 25 ml). The extracts were washed with water and saturated brine, dried and evaporated. The residual solid was recrystallised from a mixture of water and ethanol to give the title acid (0.342g), with m.p. 177-180°.

Example 15

4-[3-(4-Acetyl-3-hydroxy-2-propylphenoxy)propoxy]-2-hydroxy-N-1H-tetrazol-5-yl-benzamide

The title compound (m.p. 248-250°, from a mixture of water ~ thylformamide) was prepared by a similar procedure to Example 3, from the compound of Example 12a.



Example 164-[9-(4-Acetyl-3-hydroxy-2-propylphenoxy)nonyloxy]-2-hydroxybenzoic acid hemihydrate

The title compound, m.p. 92-94° (from a mixture of ethanol and 0.1 N hydrochloric acid) (methyl ester had m.p. 70-72°); was prepared by a similar procedure to Example 2 from the compound of Preparation 21 and 2,4-dihydroxybenzoic acid, methyl ester.

Example 1710 4-[3-[4-Acetyl-3-hydroxy-2-propylphenoxy]propoxy]-2-hydroxybenzoic acid

The compound of Preparation 37 (1.1g) was hydrogenated at atmospheric pressure in ethanol (75 ml) using 5% platinum on charcoal (45 mg) as the catalyst. When the uptake of hydrogen was complete the mixture was filtered and the filtrate was evaporated to dryness. The residue was recrystallised from toluene to give the title acid (0.78g), with m.p. 173-174°.

Example 1820 4-[3-[4-Acetyl-3-hydroxy-2-(2-propenyl)phenoxy]propoxy]-2-hydroxybenzoic acid

The compound of Preparation 37 (1.0g) was heated under reflux with 2N sodium hydroxide (3ml) and methanol (30 ml) for 24h. The mixture was poured into water (100 ml), acidified and the solid was filtered off, dried and recrystallised from toluene to give the title acid (0.62g), with m.p. 180-181° (dec.).

Example 1930 4-[3-(4-Acetyl-3-hydroxy-2-propylphenoxy)propoxy]-2-hydroxybenzoic acid

Methyl 2,4-dihydroxybenzoate (0.51g), the compound of Preparation 29 (1g) and potassium carbonate (0.83g) were heated under reflux in butanone (20 ml) for 7.25h. The mixture was cooled and filtered. The residue was washed with butanone and the combined filtrate and washings

were evaporated to give a solid which was recrystallised from methanol to give the methyl ester of the title compound (0.8g), with m.p. 99 - 100.5°.

The ester (0.76g) was heated under reflux with 2N sodium hydroxide (4.75 ml) and methanol (50 ml) for 18h. The mixture was evaporated to dryness and the residue dissolved in water (100 ml). The solution was washed with ethyl acetate, acidified with 2N hydrochloric acid and extracted with ethyl acetate (3 x 50 ml). The combined extracts were washed with water and saturated brine, dried and evaporated to dryness. The solid residue was recrystallised three times from toluene, with charcoal decolourisation, to give the title acid (0.4g), with m.p. 173 - 175°.

Example 20

4-[5-(4-Acetyl-3-hydroxy-2-propylphenoxy)propoxy]-2-methoxybenzoic acid

The title compound, m.p. 110 - 112° (from a mixture of petroleum ether and toluene) (methyl ester had m.p. 79 - 81°); was prepared by a similar procedure to Example 12a from the compound of Preparation 36 and 1-[2,4-dihydroxy-3-propylphenyl]ethanone.

Example 21

4-[5-(4-Acetyl-3-hydroxy-2-propylphenoxy)propoxy]-5-bromo-2-hydroxybenzoic acid

The title compound m.p. 172-173° (from toluene) (methyl ester had m.p. 120 - 122° (from a mixture of petroleum ether and ethyl acetate)); was prepared by a similar procedure to Example 12a from the compound of Preparation 27 and 1-[2,4-dihydroxy-3-propylphenyl]ethanone.

Example 22

4-[5-(4-Acetyl-3-hydroxy-2-propylphenoxy)propoxy]-2-hydroxy-5-nitrobenzoic acid

The compound m.p. 197-198° (from a mixture and water) (methyl ester had m.p. 89 - 91° (from



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a mixture of petroleum ether and ethyl acetate)); was prepared by a similar procedure to Example 12a from the compound of Preparation 28 and 1-[2,4-dihydroxy-3-propylphenyl]ethanone.

Pharmaceutical Examples

<u>Tablets</u>	Direct Compression	mg/tablet
Active ingredient	100.00	
Microcrystalline Cellulose B.P.C	298.00	
Magnesium Stearate	2.00	
Compression Weight	400.00	

The active ingredient is sieved through a 250 µm sieve, blended with the excipients and compressed using 10.0mm punches.

<u>Capsules</u>	mg/capsule
Active Ingredient	100.00
STA-RX 1500	99.00
Magnesium Stearate B.P.	1.00

The active ingredient is sieved through a 250 µm sieve and blended with the other materials. The mix is filled into No.2 hard gelatin capsules.

<u>Inhalation Cartridges</u>	/ cartridge
Active Ingredient (micronised)	10mg
Lactose B.P. to	25mg

The active ingredient is micronised so that the majority of particles are between 1 µm and 5 µm in longest dimension and none are greater than 10 µm. The active ingredient is then blended with the lactose and the mix is filled into No.3 hard gelatin capsules.

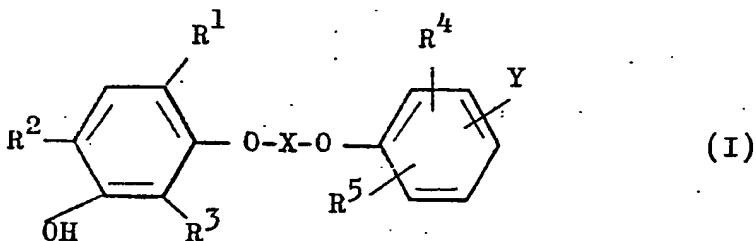
The ability of the compounds to act as antagonists of the action of SRS-A was shown using guinea-pig isolated ileum according to the methods of Coleman et al, Br. J. Pharmacol., (1979), 66, 83P. Compounds were tested at 5 concentrations of 10^{-6} M and pA₂ values were determined using the standard procedures of Arunlakshana and Schild, Br. J. Pharmac. Chemother., (1959), 14, 48 - 58:

	Example No.	pA ₂	Example No.	pA ₂
10	1g	7.0	5	7.3
	2a	7.4	8	7.8
	2c	7.4	9b	7.5
	4b	7.3	10b	7.1

The compounds are in general non-toxic at 15 therapeutically useful doses. For example, the compounds of Examples 2a, 5 and 8, when given orally to dogs at doses of up to 10 mg/kg, produced no adverse effects.

CLAIMS:

1. A compound of the general formula (I)



wherein

Y represents the group -A, -ZA or OZ¹A

wherein A represents a carboxylic acid group; a 5-1H-tetrazolyl ring or a N-5-1H-tetrazolylcarboxamide group;

Z represents a C₁₋₄ alkylene, C₂₋₄ alkenylene or C₂₋₄ alkynylene chain optionally substituted by one or more C₁₋₃ alkyl groups and Z¹ represents a C₁₋₄ alkylene chain optionally substituted by one or more C₁₋₃ alkyl groups;

X represents a C₁₋₁₀ carbon chain which may be saturated or unsaturated in the case of chains containing at least 4 carbon atoms, and may be substituted by a hydroxyl group or by one or more C₁₋₃ alkyl groups, which chain may be interrupted by a benzene ring which may be linked through its 1- and 2-, 1- and 3-, or 1- and 4-positions;

R¹ represents a hydrogen atom or a C₁₋₆ alkyl group;

R² represents the group -COR⁶ where R⁶ represents a hydrogen atom, an aryl group, or a C₁₋₆ alkyl group which may be substituted by an aryl group;

R^3 represents a C_{1-6} alkyl group or a C_{7-6} alkenyl group; and R^4 and R^5 which may be the same or different, each represents a hydrogen atom, a halogen atom or a hydroxy, C_{1-3} alkoxy, C_{1-6} alkyl, C_{3-6} alkenyl, C_{1-5} alkanoyl, nitro or carboxylic acid group with the proviso that R^4 and R^5 cannot both be nitro, alkanoyl or carboxylic acid groups, and physiologically acceptable salts thereof.

2. A compound according to claim 1, wherein in the general formula (I):

Y represents a carboxylic acid group or a 5-1H-tetrazolyl ring or the group ZA or OZ^1A where A is a carboxylic acid group and Z is a C_{1-4} alkylene chain, a C_{2-4} alkenylene chain or a C_{2-4} alkynylene chain and Z^1 is methylene;

X represents a straight carbon chain of formula $-(CH_2)_n$ where n is a number from 1 to 10, or a group of formula $-CH_2X^1CH_2-$ where X is a benzene ring linked through its 1- and 2-, 1- and 3- or 1- and 4-positions; n^1 represents a hydrogen atom or a C_{3-6} alkyl group;

R^2 represents the group COR^6 where R^6 represents a C_{1-6} alkyl group;

R^5 represents a C_{3-6} alkyl or C_{7-6} alkenyl group;

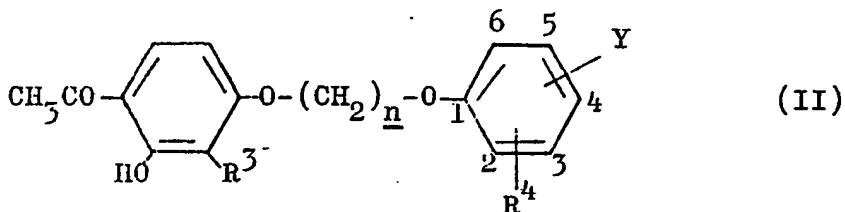
R^4 represents a hydrogen or halogen atom or a hydroxy, nitro or C_{1-3} alkanoyl group; and

R^5 represents a hydrogen atom or a C_{1-6} alkyl group or a C_{2-4} alkenyl group.

and according to claim 1 or 2 wherein the general formula (I), R^4 represents a hydrogen

atom or a hydroxyl group and R⁵ is a hydrogen atom.

4. A compound of the general formula (II)



wherein Y is a carboxylic acid group or a 5-1H-tetrazolyl ring or a N-5-1H-tetrazolyl-carboxamide group or a C₁₋₂-alkyl, C₁₋₂ alkoxy or C₂-alkenyl chain terminally substituted by a carboxylic acid group;

R³ represents a C₃₋₆ alkyl or a C₃₋₆ alkenyl group,

R⁴ represents a hydrogen or bromine atom or a hydroxy, nitro or acetyl group, and n is 1, 3 or 5, and physiologically acceptable salts thereof.

5. A compound according to claim 4, wherein in the general formula (II) Y, is situated at the 3- or 4-position in the benzene ring.

6. A compound according to claim 4 or 5, wherein in the general formula (II) n is 3.

7. 4-[3-(4-Acetyl-3-hydroxy-2-propylphenoxy)propoxy]-2-hydroxybenzoic acid and its physiologically acceptable salts.

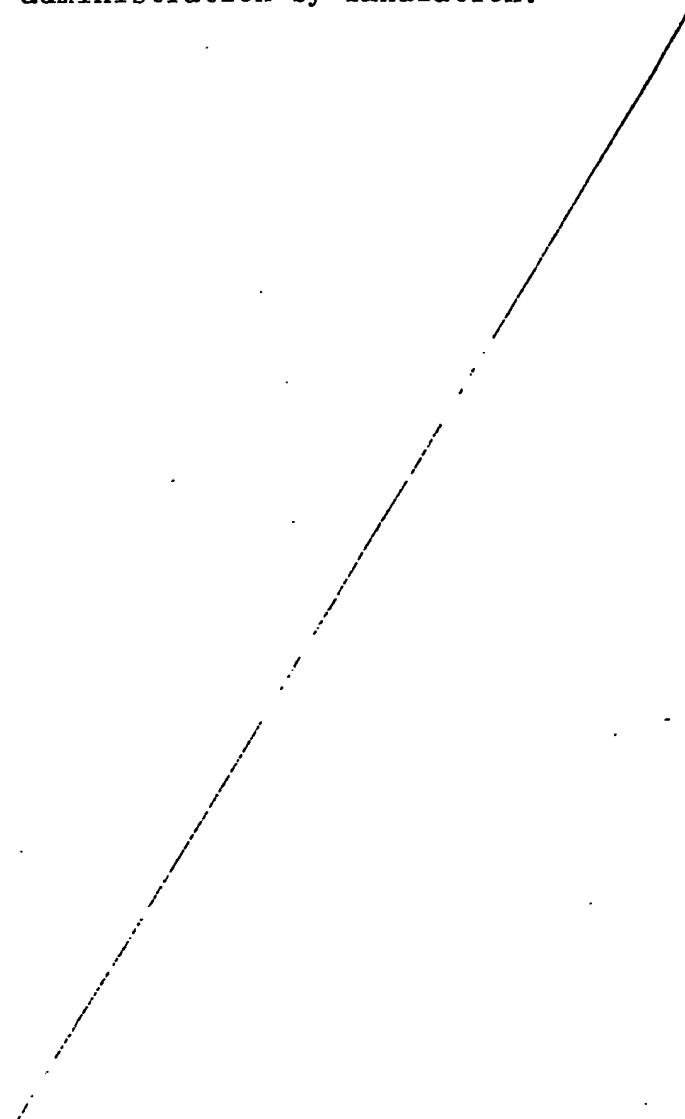
8. 4-[3-(4-Acetyl-3-hydroxy-2-propylphenoxy)propoxy]-2-hydroxy-N-1H-tetrazol-5-yl-benzamide and its physiologically acceptable salts.

9. A pharmaceutical composition comprising, as active ingredient, one or more compounds according to any of claims 1 to 8 together with one or more physiologically acceptable carriers or excipients therefor.

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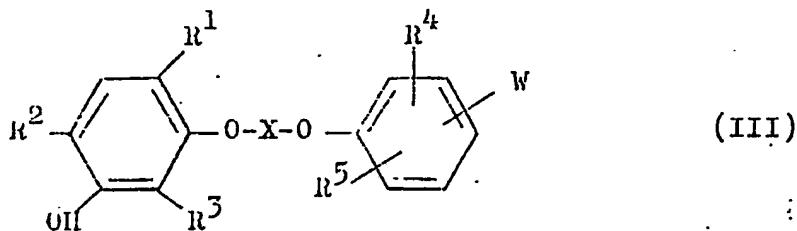
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10. A pharmaceutical composition according to
claim 9 which is formulated as a powder in a form
suitable for administration by inhalation.



11. A process for the preparation of a compound of general formula (I) as defined in claim 1 or a physiologically acceptable salt thereof which comprises the steps:

A(i) in order to prepare a compound of general formula (I), in which -Y represents the group $-\text{CH}=\text{CHCO}_2\text{H}$, subjecting a compound of general formula (III)



in which R^1 to R^5 and X are as defined in claim 1 and W represents $-\text{CH}=\text{CHCO}_2\text{H}$, to the Perkin synthesis of cinnamic acids; or
 A(ii) in order to prepare a compound of general formula (I) in which Y represents the group $-\text{A}$, $-\text{ZA}$ or $-\text{OZ}^1\text{A}$ where Z and Z^1 are as defined in claim 1 and A is a carboxylic acid group, subjecting a compound of general formula (III) where W represents the group $-\text{E}$, $-\text{ZE}$ or $-\text{OZ}^1\text{E}$ where E is a carboxylic ester, amide or nitrile group, to acid or base hydrolysis; or
 A(iii) in order to prepare a compound of general formula (I) where Y represents the group $-\text{A}$, $-\text{ZA}$ or $-\text{OZ}^1\text{A}$ where Z and Z^1 are as defined in claim 1 and A is a 5-1H-tetrazolyl ring, reacting a compound of general formula (III) in which W represents $-\text{E}$, $-\text{ZE}$ or $-\text{OZ}^1\text{E}$ and E represents a nitrile, with sodium azide and ammonium chloride; or

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A(iv) in order to prepare a compound of general formula (I) in which Y represents the group -A, -ZA or -OZ¹A where A is a carboxylic acid group and Z and Z¹ are as defined in claim 1, subjecting to hydrogenolysis a compound of general formula (III) in which W represents the group -E, -ZE or -OZ¹E and E is a carboxylic ester group of formula -COOR⁷ where R⁷ is a group removable by hydrogenolysis; or
A(v) in order to prepare a compound of general formula (I) in which Y represents the group -ZA where Z is a C₂₋₄ alkylene or C₂₋₄ alkenylene chain, subjecting another compound of general formula (I) where Z is a C₂₋₄ alkenylene or C₂₋₄ alkynylene chain to catalytic hydrogenation; or
A(vi) in order to prepare a compound of general formula (I) in which Y represents the group -A, -ZA or -OZ¹A where Z and Z¹ are as defined in claim 1 and A is a N-5-1H-tetrazolyl-carboxamide, reacting another compound of general formula (I) where A represents a carboxylic acid group with 5-amino-tetrazole in the presence of a coupling agent; and B(i) if desired reacting the resulting free acid of general formula (I) with a base to form a physiologically acceptable salt of the compound of general formula (I).



European Patent
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EUROPEAN SEARCH REPORT

0028063

Application number

EP 80 30 3101.2

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
	<p><u>GB - A - 1 144 906</u> (FISONS PHARMACEUTICAL)</p> <p>* claim 1; page 1, lines 6 to 10 *</p> <p>--</p> <p><u>GB - A - 1 405 254</u> (MILES LABORATORIES)</p> <p>* claim 1 *</p> <p>--</p> <p><u>DE - A1 - 2 749 518</u> (MAY & BAKER)</p> <p>* claims 1 and 13 *</p> <p>-----</p>	1-4, 9 1 1,8, 9 . / ..	C 07 C 65/32 C 07 C 59/84 C 07 C 79/46 C 07 C 79/38 C 07 D 257/04 C 07 D 257/06 A 61 K 31/04 A 61 K 31/12 A 61 K 31/19 A 61 K 31/21 A 61 K 31/40 C 07 C 51/08 C 07 C 51/09 TECHNICAL FIELDS SEARCHED (Int.Cl.) A 61 K 31/04 A 61 K 31/12 A 61 K 31/19 A 61 K 31/21 A 61 K 31/40 C 07 C 51/08 C 07 C 51/09 C 07 C 51/235 C 07 C 51/36 C 07 C 59/52 C 07 C 59/64 C 07 C 59/84 C 07 C 65/105 C 07 C 65/21 CATEGORY OF CITED DOCUMENTS X: particularly relevant A: technological background O: non-written disclosure P: intermediate document T: theory or principle underlying the invention E: conflicting application D: document cited in the application L: citation for other reasons &: member of the same patent family, corresponding document
N	The present search report has been drawn up for all claims		
Place:	Berlin	Date of completion of the search 06-01-1981	Examiner KNAACK



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Application number

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DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int. CL.)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
			C 07 C 51/235 C 07 C 51/36
TECHNICAL FIELDS SEARCHED (Int. CL.)			
			C 07 C 65/32 C 07 C 79/38 C 07 C 79/46 C 07 D 257/04 C 07 D 257/06